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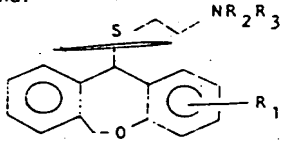
(54) **Dibenz(b,e)oxepin derivatives and pharmaceutical compositions containing them.**

(57) A pharmaceutical composition contains, as the active ingredient, a dibenz [b,e] oxepin derivative represented by the following formula:

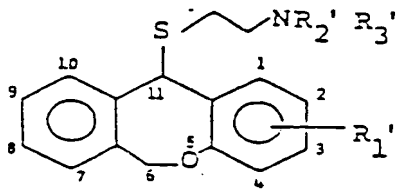


wherein R_1 represents an alkyl group having 1 to 5 carbon atoms or a halogen atom; R_2 and R_3 may be same or different group and each represent an alkyl group having 1 to 5 carbon atoms and the pharmaceutically acceptable acid addition salts thereof.

EP 0 085 870 A1

This invention relates to novel dibenz[b,e]-oxepin derivatives, the pharmaceutically acceptable acid addition salts thereof and a pharmaceutical composition containing, as the active ingredient, a dibenz[b,e]-oxepin derivative.

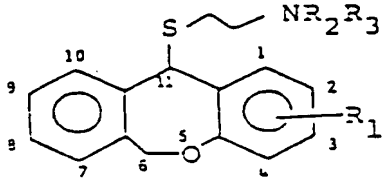
More particularly, the present invention pertains to a novel dibenz[b,e]oxepin derivative represented by the following general formula (Ia):



(Ia)

wherein R_1' represents an alkyl group having 1 to 5 carbon atoms or a halogen atom, R_2' and R_3' may be same or different group and each represent an alkyl group having 1 to 5 carbon atoms; provided that when R_2' and R_3' represent a methyl group, R_1' does not represent a methyl group, a fluorine atom, a chlorine atom or a bromine atom; and the pharmaceutically acceptable acid addition salts thereof.

In addition, the present invention pertains to a pharmaceutical composition comprising a pharmaceutical carrier and, as an active ingredient, an effective amount of a dibenz[b,e]oxepin derivative represented by the following general formula (I)



(I)

wherein R_1 represents an alkyl group having 1 to 5 carbon atoms or a halogen atom, R_2 and R_3 may be same or different group and each represent an alkyl gorup having 1 to 5 carbon atoms; and the pharmaceutically acceptable acid addition salts thereof.

A dibenz[b,e]oxepin derivative of the present invention and the pharmaceutically acceptable acid addition salts thereof have antiasthmatic activity and are therefore useful as an antiasthmatic agent.

Among the compounds represented by the general formula (I), compounds wherein R_2 and R_3 represent a methyl group and R_1 represents a methyl group, a fluorine atom, a chlorine atom or a bromine atom are known compounds which are described in Eur. J. Med. Chem. Chimica Therapeutica 9, 259 (1974). While it is described in the reference that such compounds have antidepresant and peripheral anticholinergic activities, it is not disclosed or suggested that the compounds have an antiasthmatic activity.

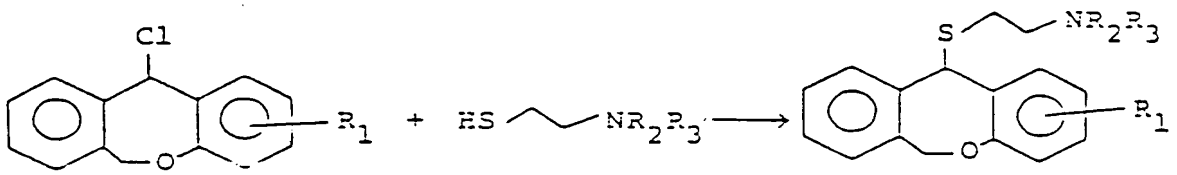
The present inventors have first found that compound I has an antiasthmatic activity.
The present invention is described in detail below.

In the definition of R_1', R_2' and R_3' in the general formula (Ia) and R_1, R_2 and R_3 in the general formula (I), the alkyl group having 1 to 5 carbon atoms includes a methyl group, an ethyl group, a propyl group, a butyl group, an amyl group, etc.; and the halogen atom includes a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom.

The acid addition salts of the general formulae (Ia) and (I) include inorganic acid addition salts such as hydrochloride, sulfate, hydrobromide, phosphate, etc. and

organic acid addition salts such as acetate, maleate, fumarate, tartrate, citrate, oxalate, benzoate, etc.

A process for production of a compound represented by the general formula (I) (hereinafter referred to as compound I) is shown below.



Compound II Compound III Compound I

wherein R_1, R_2 and R_3 have the same meanings as defined above.

Equimolecular quantities of compound II and compound III (or an acid addition salt of compound III) are dissolved in an inert solvent such as chloroform, methylene chloride, toluene, tetrahydrofuran, N,N-dimethylformamide, etc. and the mixture is stirred at room temperature to the boiling point of the inert solvent used for 30 minutes to 2 hours. Then, the solvent is removed from the reaction solution to obtain a crude salt of compound I as a residue.

The crude product is dissolved in an aqueous basic solution, and then the mixture is extracted with an organic solvent hard to be mixed with water such as diethylether, whereby the desired compound is obtained in the form of free base. Because of unlikeliness to crystallize, the product, if necessary, is subjected to purification by column chromatography, etc. and then, an appropriate acid is added thereto to obtain an acid addition salt thereof, which is more tractable. Further if necessary, the acid addition salt may be converted to a highly-purified preparate by a suitable recrystallization operation. It goes, without saying, that the aforesaid residual crude product after removal of the reaction solvent is immediately subjected to a recrystallization treatment without the liberation process whereby a purified preparate is obtained.

As an appropriate acid, a physiologically usable inorganic acid such as hydrochloric acid, sulfuric acid, hydrobromic acid and phosphoric acid or an organic acid such as acetic acid, maleic acid, fumaric acid, tartaric acid, citric acid, oxalic acid and benzoic acid may be used. Compound II, an starting material for compound I is a known compound which is disclosed in Japanese Published Unexamined Patent Application Nos. 150082/81 and 150083/81, and compound III is on the market and readily available. Results of acute toxicity test and antiasthmatic activity test of compound I are shown below.

Acute toxicity test

Groups of male dd-strain mice (each group consisting of five mice) weighing 20 ± 1 g are used. Compound I are administered orally (po : 0.3 mg/g) or intraperitoneally (ip : 0.1 mg/g). The MLD (minimum lethal dose) is calculated from the mortality for 7 days after the administration to obtain the results given in Table 1.

Table 1

Compound	MLD (mg/Kg)	
	po	ip
Compound 1	>300	>100
" 2	>300	>100
" 3	>300	>100
" 4	>300	>100
" 5	>300	100
" 6	>300	>100
" 7	>300	>100
" 8	>300	>100
" 9	>300	>100
" 10	>300	>100
" 11	>300	>100

Typical examples (compounds 1 - 11) of compound I are designated as follows.

Compound	Name of compound
1	2-methyl-11-[2-(dimethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin
2	2-methyl-11-[2-(diethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin
3	4-methyl-11-[2-(diethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin
4	2-chloro-11-[2-(diethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin
5	2-ethyl-11-[2-(diethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin
6	2-fluoro-11-[2-(diethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin
7	2-ethyl-11-[2-(dimethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin
8	2-fluoro-11-[2-(dimethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin
9	2-ethyl-11-[2-(diisopropylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin
10	2-fluoro-11-[2-(diisopropylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin
11	3-methyl-11-[2-(dimethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin

Antiasthmatic activity test

[Experimental method]

Antiasthmatic activity is evaluated according to passive cutaneous anaphylaxis response (PCA response). Antiserum is collected from Wistar strain male rats weighing 200 to 250 g. PCA response is evaluated using Wistar strain

male rats weighing 100 to 120 g.

(A) Preparation of antiserum:

One mg of egg albumin is dissolved in 0.5 ml of pertussisdiphtheria mixed vaccine, and the resulting solution is mixed with 0.5 ml of incomplete adjuvant. The resulting emulsion is used as antigen and administered to rats subcutaneously through the sole. On the 12th day after the administration, heads of the rats are cut to collect blood. Thus, antiserum is prepared.

Upon evaluating antiasthmatic activity, concentration of the antiserum is adjusted so that diameter of blue-dyed portion is about 8 to about 10 mm.

(B) PCA response (evaluation of antiasthmatic activity):

Six rats are used per group. 0.05 ml of the antiserum is intracutaneously administered to each of the previously back-shaved rats to sensitize. After 17 hours, compound I or the solutions thereof (physiological salt solution or CMC solution) are respectively administered and, after 60 minutes, an antigen mixture (1% Evans' Blue physiological salt solution containing 0.2% egg albumin) is injected intravenously in an amount of 0.5 ml/100 g to induce PCA response. After 30 minutes, rats are choked to death followed by cutting out skin to measure the diameter of blue-dyed portion. The results are evaluated by awarding a score according to the diameter of blue-dyed portion. Furthermore, ratios of the diameters to that of solvent (physiological salt solution or CMC) administered group are determined. Compounds showing a depressing ratio of 50% or more calculated according to the following formula are concluded to show positive antiasthmatic activity. Also, the minimum effective dose (MED) is determined from the results with respective doses to compare the strength of antiasthmatic activity. Results thus obtained are tabulated in Table 2.

Score	Blue-dyed Portion (ø mm)
5	≥ 10 mm
4	8.0 - 9.9 "
3	6.0 - 7.9 "
2	4.0 - 5.9 "
1	2.0 - 3.9 "
0	0 - 1.9 "

Depressing ratio (%) =

$$\frac{\text{Diameter for solvent-administered group} - \text{Diameter for test compound-administered group}}{\text{Diameter for solvent-administered group}} \times 100$$

Table 2

Compound \ Dose mg/Kg PO	100	50	25	10	5	2.5	1	MED mg/Kg PO
Compound 1	100	100	100	100	100	81	49	2.5
" 2	100	100	100	52	40	20	-	10.0
" 3	52	14	-	-	-	-	-	100.0
" 4	100	100	46	10	-	-	-	50.0
" 5	100	100	100	56	36	-	-	10.0
" 6	100	100	84	3	-	-	-	25.0
" 7	100	100	100	100	81	30	-	5.0
" 8	100	100	100	33	23	-	-	25.0
" 9	100	100	67	22	-	-	-	25.0
" 10	73	11	11	0	-	-	-	100.0
" 11	61	61	28	0	-	-	-	50.0

As is apparent from Table 2, compound I has an antiasthmatic activity and is useful as an antiasthmatic agent.

Compound I may be used in various pharmaceutical forms for administration. Pharmaceutical compositions of the present invention are prepared by uniformly mixing an effective amount of compound I as the active ingredient, in free form or as an acid addition salt, with a pharmaceutically acceptable carrier.

The carrier may take various forms depending on the pharmaceutical form suitable for administration. It is preferable that the pharmaceutical composition is in single administration form suitable for administration orally or by injection.

To prepare the compositions of the present invention for oral administration, any useful pharmaceutical carrier may be used. For example, oral liquid preparations such as suspensions and syrups can be prepared using water, sugar (e.g. sucrose, sorbitol and fructose), glycols (e.g. polyethyleneglycol and propyleneglycol), oils (e.g. sesame oil, olive oil and soybean oil), antisepics (e.g. an alkyl parahydroxybenzoate), flavours (e.g. strawberry flavour and peppermint) and the like. Powders, pills, capsules and tablets can be prepared using excipients (e.g. lactose, glucose, sucrose and mannitol), disintegrators (e.g. starch and sodium alginate), lubricants (e.g. magnesium stearate and talc), binders (e.g. polyvinyl alcohol, hydroxypropylcellulose and gelatin), surfactants (e.g. sucrose fatty acid ester), plasticizers (e.g. glycerin) and the like.

Tablets and capsules are the most useful single oral administration forms because of the ease of administration. To make tablets and capsules solid pharmaceutical carriers are used.

An injection solution can be prepared using a carrier consisting of salt solution, glucose solution and a mixture of salt and glucose solution.

Although the amount of the active ingredient can be varied over a rather wide range, 1 - 20 mg/kg/day in one

dose or several divided doses is generally considered to be effective.

Certain specific embodiments of the invention are illustrated by the following representative examples.

Example 1

In this example, 1.70 g of diethylaminoethyl-thiolhydrochloride and 2.45 g of 2-methyl-11-chloro-6,11-dihydrodibenz[b,e]oxepin are dissolved in 50 ml of methylene chloride, and the mixture is stirred for 2 hours. The reaction solution is concentrated under reduced pressure to distill off methylene chloride. Recrystallization of the residue from 50 ml of ethanol gives 3.25 g of pure crystals of hydrochloride of 2-methyl-11-[2-(diethylamino)-ethyl]thio-6,11-dihydrodibenz[b,e]oxepin (compound 2) in a yield of 86%.

m.p.: (hydrochloride) 202 - 205°C

IR absorption spectrum: (KBr tablet, cm^{-1})
2920, 2670, 1495, 1260, 1230, 1015

Elemental analysis of hydrochloride:

	C(%)	H(%)	N(%)
Calcd. for $C_{21}H_{27}NOS \cdot HCl$:	66.73	7.47	3.71
Found:	66.52	7.23	3.90

The resulting hydrochloride is dissolved in a basic water, and then the solution is extracted with diethylether. The extract is dehydrated and concentrated to obtain an oily free base.

NMR spectrum ($CDCl_3$, δvalue, ppm): 0.93(t, 6H), 2.22(s, 3H), 1.93 - 2.79(m, 8H), 4.77(d, 1H), 4.89(s, 1H), 6.23(d, 1H), 6.52 - 7.45(m, 7H)

Examples 2 to 11

Compounds 1 and 3 through 11 having the physico-chemical properties identified in Tables 4 and 5 are obtained in a similar manner to that in Example 1 except that the amino-

ethylthiolhydrochloride and 11-chloro-6,11-dihydrobenz-[b,e]oxepin shown in Table 3 are used instead of diethyl-aminoethylthiolhydrochloride and 2-methyl-11-chloro-6,11-dihydrodibenz[b,e]oxepin in Example 1.

Table 3

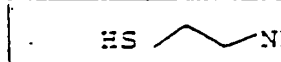
Example	Aminoethylthiolhydrochloride		
			Used amount (g)
	R_2	R_3	
2	methyl	methyl	1.4
3	ethyl	ethyl	1.0
4	ethyl	ethyl	1.4
5	ethyl	ethyl	1.7
6	ethyl	ethyl	1.7
7	methyl	methyl	1.4
8	methyl	methyl	1.4
9	isopropyl	isopropyl	2.0
10	isopropyl	isopropyl	2.0
11	methyl	methyl	2.8

Table 3 (.../... contd.)

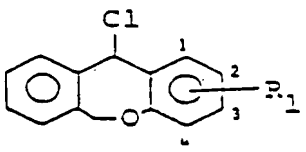
Example	11-chloro-6,11-dihydrodibenz[b,e]oxepin	Used amount (g)
		
	R_1	
2	2-methyl	2.4
3	4-methyl	1.4
4	2-chloro	2.2
5	2-ethyl	2.6
6	2-fluoro	2.5
7	2-ethyl	2.6
8	2-fluoro	2.5
9	2-ethyl	2.6
10	2-fluoro	2.5
11	3-methyl	5.2

Table 4

Example	Compound	Obtained amount of the desired compound (g)	Yield (%)	Physicochemical properties	
				m.p. (°C) (hydrochloride)	IR absorption spectrum (hydrochloride, KBr tablet, cm^{-1})
2	Compound 1	1.8	51	166 - 169	2690, 1500, 1460, 1260, 1230, 1015
3	" 3	2.1	97	163 - 165	2920, 2580, 2470, 1470, 1195, 1010
4	" 4	3.1	93	165 - 167	2920, 2620, 1485, 1255, 1230, 1020
5	" 5	3.6	90	157 - 160	2920, 2670, 1500, 1255, 1235, 1010
6	" 6	3.6	94	134 - 137	2920, 2620, 1495, 1255, 1210, 1025
7	" 7	2.9	80	149 - 151	2920, 1505, 1260, 1230, 1125, 1020
8	" 8	3.2	90	169 - 172	2920, 2720, 1500, 1260, 1230, 1025
9	" 9	3.8	98	hydrochloride being unable to crystallize, and fumarate being too hygroscopic to measure	Oily free base, NaCl cell 2970, 1500, 1260, 1230, 1120, 1020
10	" 10	3.7	98	"	Oily free base, NaCl cell 2970, 1500, 1260 1225, 1160, 1020
11	" 11	6.1	98	155 - 158	2920, 2660, 1620 1460, 1260, 1125

Table 5

Example	NMR spectrum ($CDCl_3$, δ : ppm)	Elemental analysis Calcd.(%)	Found(%)
2	Oily free base 2.14(s,6H), 2.23(s,3H), 1.97-2.77(m,4H), 4.77(d,1H), 4.90(s,1H), 6.22(d,1H), 6.59-7.39(m,7H)	$C_{19}H_{23}NOS \cdot HCl$ C 65.22 H 6.91 N 4.00	 65.20 6.84 3.89
3	Hydrochloride 1.22(t,6H), 2.20(s,3H), 2.6-3.4(m,9H), 4.89(d,1H), 5.10(s,1H), 6.00(d,1H), 6.6-7.5(m,7H)	$C_{21}H_{27}NOS \cdot HCl$ C 66.73 H 7.47 N 3.71	 66.59 7.49 3.58
4	Hydrochloride 1.27(t,6H), 2.6-3.3(m,9H), 4.83(d,1H), 5.13(s,1H), 6.12(d,1H), 6.6-7.6(m,7H)	$C_{20}H_{24}ClNOS \cdot HCl$ C 60.30 H 6.32 N 3.52	 60.03 6.17 3.66
5	Hydrochloride 0.9-1.6(m,9H), 2.3-3.5(m, 10H), 4.83(d,1H), 5.09(s, 1H), 6.07(d,1H), 6.6-7.6 (m,7H), 11.9(br,1H)	$C_{22}H_{29}NOS \cdot HCl$ C 67.41 H 7.71 N 3.57	 67.37 7.80 3.39
6	Hydrochloride 1.27(t,6H), 2.5-3.5(br,8H), 4.82(d,1H), 5.17(s,1H), 6.03(d,1H), 6.7-7.6(m,7H), 11.8(br,1H)	$C_{20}H_{24}FNOS \cdot HCl$ C 62.90 H 6.60 N 3.67	 63.01 6.74 3.51
7	Hydrochloride, $CDCl_3$ + d_6DMSO 1.17(t,3H), 2.4-3.6(m,13H), 4.87(d,1H), 5.25(s,1H), 6.03(d,1H), 6.6-7.6(m,7H)	$C_{20}H_{25}NOS \cdot HCl$ C 66.00 H 7.20 N 3.85	 66.05 6.98 3.69
8	Hydrochloride, $CDCl_3$ + d_6DMSO 2.4-3.6(m,11H), 4.80(d,1H), 5.29(s,1H), 5.97(d,1H), 6.7-7.6(m,7H)	$C_{13}H_{20}FNOS \cdot HCl$ C 61.09 H 5.98 N 3.96	 61.32 6.09 4.00

Table 5 (.../... contd.)

Example	NMR spectrum ($CDCl_3$, δ : ppm)	Elemental analysis Calcd.(%)	Found(%)
9	Oily free base 0.91(d,12H), 1.20(t,3H), 2.3-3.2(m,8H), 4.80(d,1H), 4.91(s,1H), 6.29(d,1H), 6.7-7.5(m,7H)	$C_{24}H_{33}NOS$ C 75.15 H 8.67 N 3.65	 75.02 8.58 3.77
10	Oily free base 0.93(d,12H), 2.47(s,4H), 2.7-3.2(m,2H), 4.80(d,1H), 4.85(s,1H), 6.22(d,1H), 6.7-7.5(m,7H)	$C_{22}H_{28}FNOS$ C 70.74 H 7.56 N 3.75	 70.49 7.31 3.84
11	Hydrochloride, $CDCl_3$ + d_6DMSO 2.22(s,3H), 2.4-3.3(m,11H), 4.82(d,1H), 5.23(s,1H), 6.12(d,1H), 6.5-7.6(m,7H)	$C_{19}H_{23}NOS \cdot HCl$ C 65.22 H 6.91 N 4.00	 65.08 7.03 3.88

Example 12 : Preparation of tablet

A tablet comprising the following components is prepared in a conventional manner.

Component	
Hydrochloride of compound 1	30 mg
Lactose	60 mg
Potato starch	30 mg
Polyvinyl alcohol	2 mg
Magnesium stearate	1 mg
Tar pigment	q.s.

Example 13 : Preparation of powder

A powder comprising the following components is prepared in a conventional manner.

Component	
Hydrochloride of compound 2	30 mg
Lactose	270 mg

Example 14 : Preparation of syrup

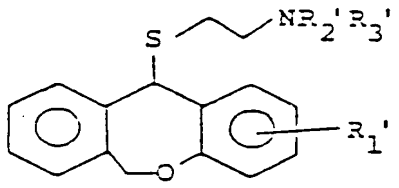
A syrup comprising the following components is prepared in a conventional manner.

Component	
Hydrochloride of compound 7	300 mg
Sucrose	40 g
Methyl para-hydroxybenzoate	40 mg
Propyl para-hydroxybenzoate	10 mg
Strawberry flavour	0.1 cc

Water is added to the above components until the total volume is 100 cc.

WHAT IS CLAIMED IS:

1. A novel dibenz[b,e]oxepin derivative represented by the following general formula (Ia):



(Ia)

wherein R_1' represents an alkyl group having 1 to 5 carbon atoms or a halogen atom; R_2' and R_3' may be same or different group and each represent an alkyl group having 1 to 5 carbon atoms provided that when R_2' and R_3' represent a methyl group, R_1' does not represent a methyl group, a fluorine atom, a chlorine atom or a bromine atom; and the pharmaceutically acceptable acid addition salts thereof.

2. A derivative of claim 1; namely, 2-methyl-11-[2-(diethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin.

3. A derivative of claim 1; namely, 4-methyl-11-[2-diethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin.

4. A derivative of claim 1; namely, 2-chloro-11-[2-(diethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin.

5. A derivative of claim 1; namely, 2-ethyl-11-[2-(diethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin.

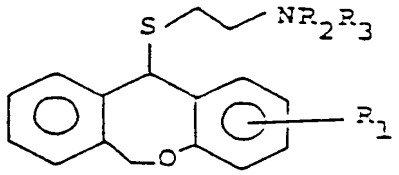
6. A derivative of claim 1; namely, 2-fluoro-11-[2-(diethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin.

7. A derivative of claim 1; namely, 2-ethyl-11-[2-(dimethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin.

8. A derivative of claim 1; namely, 2-ethyl-11-[2-(diisopropylamino)ethyl]thio-6,11-dihydrodibenz[b,e]exepin.

9. A derivative of claim 1; namely, 2-fluoro-11-[2-(diisopropylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin.

10. A pharmaceutical composition comprising a pharmaceutical carrier and, as an active ingredient, an effective amount of a dibenz[b,e]oxepin derivative represented by the following general formula (I)



(I)

wherein R_1 represents an alkyl group having 1 to 5 carbon atoms or a halogen atom, R_2 and R_3 may be same or different group and each represent an alkyl group having 1 to 5 carbon atoms; and the pharmaceutically acceptable acid addition salts thereof.

11. A pharmaceutical composition according to claim 10, wherein said dibenz[b,e]oxepin derivative is 2-methyl-11-[2-(dimethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin.

12. A pharmaceutical composition according to claim 10, wherein said dibenz[b,e]oxepin derivative is 2-methyl-11-[2-(diethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin.

13. A pharmaceutical composition according to claim 10, wherein said dibenz[b,e]oxepin derivative is 4-methyl-11-[2-(diethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin.

14. A pharmaceutical composition according to claim 10, wherein said dibenz[b,e]oxepin derivative is 2-chloro-11-[2-(diethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin.

15. A pharmaceutical composition according to claim 10, wherein said dibenz[b,e]oxepin derivative is 2-ethyl-11-[2-(diethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin.

16. A pharmaceutical composition according to claim 10, wherein said dibenz[b,e]oxepin derivative is 2-fluoro-11-[2-(diethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin.

17. A pharmaceutical composition according to claim 10, wherein said dibenz[b,e]oxepin derivative is 2-ethyl-11-[2-(dimethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin.

18. A pharmaceutical composition according to claim 10, wherein said dibenz[b,e]oxepin derivative is 2-fluoro-11-[2-(dimethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]oxepin.

19. A pharmaceutical composition according to claim 10, wherein said dibenz[b,e]oxepin derivative is 2-ethyl-11-[2-(diisopropylamino)ethyl]thio-6,11-dihdrodibenz[b,e]-oxepin.

20. A pharmaceutical composition according to claim 10, wherein said dibenz[b,e]oxepin derivative is 2-fluoro-11-[2-(diisopropylamino)ethyl]thio-6,11-dihydrodibenz[b,e]-oxepin.

21. A pharmaceutical composition according to claim 10, wherein said dibenz[b,e]oxepin derivative is 3-methyl-11-[2-(dimethylamino)ethyl]thio-6,11-dihydrodibenz[b,e]-oxepin.

European Patent Office

EUROPEAN SEARCH REPORT

0085870
Application number

EP 83 10 0533

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl. ³)
D,A	EUROPEAN JOURNAL OF MEDICAL CHEMISTRY - CHIMICA THERAPEUTICA, vol. 9, no. 3, 1974, P. DOSTERT et al. "Composes tricycliques portant une chaine alkylaminoalkylthio. Synthese et activite pharmacologique" * Pages 259-262 *	1,10	C 07 D 313/12 A 61 K 31/335
A	US-A-4 282 365 (MERCK) * Claim 1; columns 1, 2 *	1,10	
A	EP-A-0 038 564 (KYOWA HAKKO KOGYO CO. LTD.)		

TECHNICAL FIELDS SEARCHED (Int Cl ³)
A 61 K 31/335 C 07 D 313/12

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	18-04-1983	PHILLIPS N.G.A.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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